RELATION BETWEEN SENSITIVITY TO THIOPENTONE, SULPHONAMIDES, AND SUNLIGHT

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Intravenous injection of thiopentone is a very frequent and, in experienced hands, safe procedure in both anaesthetic and narcoanalytical practice. Sensitivity reactions occur infrequently, Davidson (1943) mentioning two instances in 9,000 injections. We have administered over 15,000 injections in surgical and psychiatric practice and have encountered the three cases of sensitivity reported here. Two of these involved not the scarlatiniform rash commonly seen in these uncommon cases but angioneurotic oedema, and the other showed a less developed form of the syndrome. We wish to call attention to these uncommon reactions, which could, if unprepared for and unexpected, lead to grave difficulties, especially when encountered in the consulting-room as opposed to the operating theatre. We also wish to correlate our findings with other apparently relevant evidence concerning sensitivity to sulphonamide compounds encountered therapeutically.

Case 1

A single woman aged 26 had received 15 injections of thiopentone (0.15–0.35 g.) over a period of six months from January, 1948, in the narcoanalytical treatment of the depressively coloured anxiety state associated with very severe insomnia, from which she had suffered for five years. Response to treatment had been satisfactory. Injection of thiopentone caused sleep for three to seven minutes followed by a prolonged drowsiness, without signs of sensitivity. In April, 1950, a further narcoanalytical session was occasioned by a recurrence of symptoms, and subjective relief was obtained. In May she again presented herself for narcoanalytical treatment. The day had been very sunny, but naturally she did not mention the fact that she had exposed her face and arms for 20 minutes at 3 p.m., two hours before the injection (during which no perivenous leakage occurred) of 0.35 g. of thiopentone.

Five minutes after the end of the injection, as she was rousing from the deepest sleep, her face became brilliantly red and minor restless movements of the head and neck occurred. Restlessness increased and within three to five minutes the forearms and elbow regions were reddened, the patient clasping the lower abdomen. Marked urticaria appeared above the elbows, and colic and numbness of the lips were complained of in a hoarse voice. Her face and eyelids were swollen, and pitting oedema was present over the radius. Twelve minutes after the injection the pulse was thin and thready, the rate being 146. A diagnosis of angioneurotic oedema was made, and adrenaline, 7 min. (0.4 ml.), was given subcutaneously at the rate of 1 min. (0.06 ml.) a minute with no good effect. At this stage the eyelids were beginning to evert and the eyes were completely closed. The lips and the tongue were swollen, and tenderness and pain were felt in the throat as well as in the abdomen; but breathing was not embarrassed, and cyanosis was absent.

One tablet of mepyramine hydrogen maleate ("anthisan") was taken with difficulty. Calcium gluconate, 10 ml. of 10% solution, was injected into the vein at the rate of 1 ml.

a minute. By the time that 6 ml. had been administered subjective relief was noticed and erythema was subsiding. As the distribution of the skin reaction was so reminiscent of sulphonamide sun-sensitivity, the patient was asked at this point whether she had been sitting in the sun earlier in the day. A hoarse affirmative answer was obtained. Abdominal cramps persisted for a further 10–15 minutes. The blood pressure was 136/78 at the end of the injection of calcium gluconate, the pulse having fallen steadily from 156 to 110 during the time of the injection. She then began to feel cold and started to shiver, but this passed off in about ten minutes. One and a half hours after the injection of thiopentone she had recovered, apart from feeling rather shaken, drowsy, and muddle-headed.

Case 2

A woman aged 60 suddenly developed haematuria (due to papilloma of the bladder) associated with transient oedema of the lip while on holiday in Canada. After her return to England and during the succeeding four or five years she was at intervals submitted to intravenous anaesthesia on seven occasions, for purposes of cystoscopy and diathermic cautery of the papilloma. Premedication on the first three occasions was with "omnupon," 1/3 gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.). Hexobarbitone ("evipan") was used for the first two operations with no untoward sequelae. Thiopentone, 0.5 g., was used on the third occasion, its initial exhibition being followed by a red papilliform rash of the thorax and neck, and erythema of the face. Post-anaesthetic itching occurred. Some months later a second injection of thiopentone was followed by a similar reaction, with, in addition, transient mild angioneurotic oedema of the lips, which subsided spontaneously. Hexobarbitone was again used uneventfully for the fifth anaesthetic, but on the sixth occasion, in the absence of hexobarbitone, a different brand of thiopentone was used. Again the cutaneous reaction, with angioneurotic oedema, was elicited, and was well controlled by antihistaminics by mouth. On the seventh and most recent occasion hexobarbitone was given and the patient recovered uneventfully.

Case 3

A married woman aged 33, suffering from obsessional neurosis with anxiety hysteria, uneventfully received thiopentone, 0.25–0.35 g., intravenously on more than 40 occasions (at weekly intervals), reacting with sleep of one to three minutes, followed by drowsiness. After an interruption of treatment for six weeks, cough and laryngeal tickling appeared during the recovery of consciousness, and were at first thought to be due to an incipient cold which was later associated with nasal catarrh. Recovery from thiopentone, however, continued to be associated with cough and laryngeal discomfort after the infection had passed, and in a few weeks there occurred a red blotchy condition of the face and neck which persisted for 20 minutes or so. Systemic disturbances and itching were absent. Substitution of a sulphur-free intravenous barbiturate ("cyclonal sodium" brand of hexobarbitone) in place of thiopentone in equivalent dosage (0.6–0.8 g.) was followed by uneventful recovery from the induced sleep.

Comment.—These three cases illustrate sensitivity to thiopentone, and Cases 2 and 3 suggest very strongly that the sulphone radical is involved. Case 1 is, we believe, the first recorded instance of photosensitivity to thiopentone. It was, in fact, this case which prompted a search of the literature for similar cases, and led to a review of sensitivity to barbiturates and photosensitivity to sulphonamides.

Literature and Discussion

Barbiturate sensitivity, though uncommon, may manifest itself somatically (when it usually takes the form of a maculo-papular rash, possibly associated with systemic disturbance and pyrexia) and/or psychically (as excitement,

delirium, or collapse). The literature on angioneurotic oedema after barbiturates is small and scattered. Hunter (1943) briefly describes urticaria after incision of a septic finger under thiopentone, and mentions angioneurotic oedema after hexobarbitone, quoting Hower (1939) in support. We found reference in Hower only to angioneurotic oedema after pentobarbitone, which is of interest in view of Case 2. Hunter's main case is of idiosyncratic systemic reaction to thiopentone in an R.A.F. officer who had previously reacted normally to inhalation anaesthesia. From his description, the lesions appear to be restricted to the areas exposed to the sun (cf. sulphonamide sensitivity and Case 1). In Davidson's (1943) two cases the sensitivity consisted of scarlatiniform rashes, with transient pyrexia.

Knauss (1946) describes urticaria following dental extraction under thiopentone in a man aged 41 who had, a month earlier, uneventfully undergone the same procedure but with a preliminary local injection of adrenaline. Peterkin (1946) describes the occurrence of purpuric reactions of the trunk following thiopentone anaesthesia on three occasions in a man who had previously and uneventfully received inhalation anaesthesia. Following this, Warren (1946), R. H. Moore (1946), and P. H. Moore (1946) each described a case. In all three cases urticaria developed—in one instance after hysterectomy in a tuberculous patient, and in another in a man (who had 40 times uneventfully received thiopentone with or without inhalation anaesthesia in connexion with a perineal wound) when he was given 1 g. of thiopentone. In this case a subsequent administration of 0.5 g. of thiopentone combined with inhalation anaesthesia passed off uneventfully. Apart from these six cases mentioned in the literature, Lundy (1942) makes passing mention of the occurrence of urticarial reaction in thiopentone anaesthesia.

While it is recognized that barbiturates produce skin-sensitivity reactions, photosensitivity seems much less common. Stryker (1939) describes the case of a child aged 2 who developed an exfoliative dermatitis after receiving barbiturate for six weeks. Four months later the child developed an acute dermatitis of the exposed areas after playing in the sun, and was found to be excreting barbitone and porphyrins in the urine. Stryker quotes Schulzberger as considering barbiturates capable of giving rise to photosensitivity.

A local vesicular eruption (possibly generalized and exfoliative) is the commonest form of skin-sensitivity reaction to sulphonamides, and is most readily evoked by repeated topical application. Urticarial photosensitivity was noticed in Middle East troops, and Peterkin (1945) found 72% of 500 cases of sulphonamide dermatitis to be photosensitive. Watkinson and Hillis (1947) discuss the relationship between oral sulphonamides, sunlight, and the pustulation stage of vaccinal lesions in R.A.F. personnel. They found the highest incidence of sulphonamide photosensitivity associated with the pustulation stage of the lesion. Where vaccination did not take, or was refused, photosensitivity did not occur, even though exposure to sunlight and ingestion of sulphonamides were the same in all troops. They support Erskine's theory that toxins liberated from a buried focus are causative of photosensitivity.

Park and Platts (1942) described photosensitivity in 3.4% of (mainly ambulant) men exposed to strong sun and receiving oral sulphonamides. In a case of acute tonsillitis an unusually severe skin rash developed on the first day of oral sulphonamide (as opposed to the usual 8th–10th day), the rash being concentrated in the areas exposed to the sun, even though the last exposure had been three days earlier. They regard this case as having "photo-allergy" (Epstein, 1939), although Epstein's criteria are apparently not fulfilled. (These are solar reaction without oedema preceding injection of sulphonamide, and followed in ten days by spontaneous development of oedema at the site of injection, or elsewhere, or an earlier oedematous reaction in response to solar irradiation, provided that a certain "critical" amount of sulphonamide has been injected.)

Porphyrin excretion has not been fully investigated in the current literature (owing to circumstances), although the significance of coproporphyrin I as a photosensitizer is well recognized. Its presence in the excreta of patients taking sulphonamides was pointed out by Rimington and Hemmings (1938), who also mention that sulphonamide may evoke photosensitivity and promote the excretion of coproporphyrin I. They compare the clinical pictures of acute porphyrinuria and sulphonamide intoxication. The present paper may indicate the connexion between sulphonamides and thiobarbiturates with regard to sensitivity reactions.

Burckhardt (1948) has shown that burning, tanning, and specific photosensitivity provocation occur independently of each other at different light wavelengths, and that photosensitive reactions occur only in the areas actually irradiated by the provocative wave-band. Local tissue damage and, in some cases, systemic effects analogous to toxic reactions are characteristic of sunburn, and are in keeping with the presence in the circulation of a substance derived from tissue damage (? histamine-like, ? porphyrin-like). Systemic reactions generally last less than three days, and pigmentation usually begins after this time. Skin repeatedly exposed to ultra-violet radiation is less likely to burn even in the absence of pigmentation.

Correlating these observations, we put forward the hypothesis that skin-sensitivity reactions here considered depend upon the interaction of the following factors. (1) Tissue damage, as septic focus, mechanical trauma, local infection, or interference with tissue metabolism—for example, by drugs. (2) The presence of the sulphone radical, either as thiobarbiturate or as sulphonamide, locally applied or given by mouth or injection. Depending on the intensity of these two factors, local or general reactions may result. (3) Sunlight may act as a form of factor 1 when the burning effect is marked, and hence may be sufficient with factor 2 to produce a non-photosensitivity reaction. The longer rays may also, acting with factor 1 and/or factor 2, trigger off a true photosensitivity reaction. These reactions occur when a critical level (Epstein) is overstepped. The double role of sunlight seems to resolve the discord mentioned by Urbach and Gotlieb (1946) concerning skin colour and sulphonamide photosensitivity, on the basis of acclimatization to the burning rays of the sun as opposed to the tanning rays.

The case (Park and Platts, 1942) of tonsillitis shows the synergism of local tissue damage and circulating products from the throat, and in this instance the rash is described as photosensitive. From Park and Platts and from Watkinson and Hillis it is clear that skin areas not submitted to solar exposure or to mechanical trauma—for example, the bathing-drawers area—are never involved in sulphonamide photosensitivity, whereas the ischial tuberosities of bedridden patients are more susceptible than those of ambulant cases. In Case 1, a patient who burned easily in the sun, recent exposure had occurred, and presumably breakdown products were circulating. This would account for the local and general symptoms, on the hypothesis advanced above. Similarly, in Case 2 the focus of tissue damage was a necrosing papilloma of the bladder.

Clark (1943) describes a case, clearly illustrative of the interaction of local and general factors, in which the sequence was as follows: first four days, successful local treatment of skin lesion with sulphonamide in strong sun; ten days later sulphathiazole by mouth precipitated an acute reaction in the areas exposed to the sun, followed by secondary infection, for which seven days later he was given sulphadiazine by mouth, provoking a generalized scarlatiniform rash; six weeks later, after recovery, local sulphathiazole provoked a local reaction, and on the following day oral sulphathiazole provoked a reaction in the sun-exposed areas; ten weeks later local application of sulphathiazole provoked a local reaction.

It is perhaps relevant to point out here that in surgical practice thiopentone is usually given if established tissue damage exists and hence tissue-breakdown factors are

circulating. This would account for the tendency to the generalized form of sensitivity reaction. All the cases from the literature cited in this paper showed significant tissue damage related to general reactions.

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TERRAMYCIN IN INFECTIONS IN INFANTS AND CHILDREN

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"Terramycin" is a new antibiotic obtained from *Streptomyces rimosus*, an actinomycete isolated from the soil (Finlay *et al.*, 1950). Its physical and chemical properties have been studied by Regna and Solomons (1950), and it has been shown to be a stable, amphoteric substance of high potency (Linsell and Fletcher, 1950). Preliminary experimental studies (Hobby *et al.*, 1950) have shown that it is active both *in vitro* and *in vivo* against a wide variety of pathogenic organisms. It is effective against Gram-positive and Gram-negative bacteria, spirochaetes, rickettsiae, and certain of the larger viruses, yet is distinguished by its low toxicity (Finlay *et al.*, 1950; King *et al.*, 1950; Herrell *et al.*, 1950).

Terramycin is supplied in 50, 100, and 250-mg. capsules of the crystalline hydrochloride salt, and as a yellow crystalline powder which dissolves easily in a specially prepared cherry-mint-flavoured liquid to make an elixir ("terrabon") suitable for administration to infants and children. A special solution containing 25 mg. of terramycin as the crystalline hydrochloride, made up with 62.5 mg. of sodium chloride and 25 mg. of sodium borate, dissolved in 5 ml. of distilled water, is available for ophthalmic use.

This report is based on a study of the use of terramycin in various infections of infancy and early childhood. Sixty-six children were treated with this drug, no other therapy being given during its administration. The dosage was 50 mg. per lb. (450 g.) of body weight per day, the elixir being given by mouth at six-hourly intervals for a period of seven days to each of 54 patients. It was found to be extremely palatable, and no difficulties were encountered in its administration. In fact, ward sisters preferred its use to other antibiotics because it was taken so readily by infants and children. Routine white-cell estimations during the course of treatment did not show any depressant action on the total

count or on the polymorphonuclear elements. The special ophthalmic solution was used for the treatment of 12 newborn babies, and was instilled into the eyes in the following manner: one drop every minute for five minutes, followed by one drop every two minutes for ten minutes, the whole procedure being repeated three times a day.

Terramycin was used for the treatment of pneumonia (35 cases), upper respiratory tract infections (10 cases), tonsillitis (6 cases), pyuria (3 cases), and purulent conjunctivitis (12 cases).

Pneumonia

The 35 cases of pneumonia, all confirmed radiologically, showed the following age distribution:

0-5 months	..	..	6 cases	2 years	..	..	6 cases
6-11 "	..	..	7 "	3 "	..	..	5 "
1 year	..	..	11 "				

Nasopharyngeal swabs were cultured in every case, the predominating organism being shown in Table I.

TABLE I.—Predominating Organism on Culture of Nasopharyngeal Swab

Organism	No. of Cases
<i>Streptococcus viridans</i>	7
<i>Streptococcus haemolyticus</i>	5
<i>Pneumococci</i>	6
<i>Staphylococcus pyogenes</i>	2
<i>Haemophilus influenzae</i>	1
Friedländer's bacillus	1
Normal flora—no predominating organisms	13

In 23 cases the temperature fell to normal within 24 hours, in seven cases fever disappeared in 48 hours, and in one case in 72 hours. Improvement in appetite, colour, and general condition coincided with the settling of the temperature. Radiological clearing of the lungs usually took a few days longer than the disappearance of clinical signs.

One child, aged 3½ years, with a right lower lobe pneumonia, presenting characteristic clinical and radiological findings, showed no response to treatment until the dose was doubled and 100 mg. per lb. (450 g.) body weight per day was given. In this case the defervescence occurred by lysis over a period of eight days. No response to the drug was obtained in three patients (Table II), one of whom died.

TABLE II.—Details of Three Cases Not Responding to Terramycin

Case No.	Sex	Age	Dose	Diagnosis	Nasoph. Swab	Result
1	F	5/12	125 mg. 6-hrly for 7 days	R.L.L. pneumonia	<i>Staph. pyogenes</i>	Responded to "aureomycin"
2	F	3 yr.	250 mg. 6-hrly for 7 days	Broncho-pneumonia (coeliac disease)	<i>Pneumococci</i>	" "
3	M	6/52	100 mg. 6-hrly for 7 days	Broncho-pneumonia	Friedländer's bacilli; <i>pneumococci</i> ; <i>Str. haemolyticus</i>	Death. Necropsy showed collapse of left lower lobe, consolidation of right middle and lower lobes with abscesses. Pus: Friedländer

Upper Respiratory Tract Infections

Ten children with upper respiratory tract infections, classified as rhinopharyngitis, laryngitis, and otitis media, responded similarly to those in the pneumonia group, with an improvement in the clinical condition and a return of temperature to normal in 24 hours. In one child with otitis media, the discharge from the ear ceased within 24 hours, but the other ear then suppurated. Both ears were completely dry within five days of the onset of therapy.

Tonsillitis.—Six children with tonsillitis improved within 24 to 48 hours of treatment.